Assessment of cardiovascular risk associated with drugs for type 2 diabetes based on publicly available information

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Abstract

Diabetes is known as one of the risk factors for the incidence of cardiovascular events. In addition to the condition itself, it has been reported that some drugs used for the treatment of diabetes such as rosiglitazone increase the risk of cardiovascular events. There are growing concerns about the association between the use of hypoglycemic drugs and cardiovascular events, and therefore the US Food and Drug Administration (FDA) requires pharmaceutical companies to evaluate this association through clinical trials.

In general, the levels of evidence for those large clinical trials are high, because the primary end point of the trials is incidence of major adverse cardiovascular events (MACE), which is one of true end points of diabetes. However, the evidence is not always enough to reveal the association between drugs for type 2 diabetes and risk of cardiovascular events because of the following reasons. First, the study population of those large clinical trials is patients with type 2 diabetes "at high risk for cardiovascular events", not representatives of entire type 2 diabetes population. Second, hazard ratio (HR) was used as a measure to evaluate the cardiovascular risks associated with drugs for type 2 diabetes in those large clinical trials, but it has been reported that the HR has several limitations.

Against this background, in Research 1, we assessed the cardiovascular risks in general type 2 diabetes population for dipeptidyl peptidase-4 (DPP-4) inhibitors, one of

the most commonly prescribed drugs for type 2 diabetes, by meta-analysis. According to the results of large clinical trials, DPP-4 inhibitors did not show an increase in cardiovascular events compared with placebo in patients with type 2 diabetes at high risk for cardiovascular events. The present study showed that the same was true in general type 2 diabetes population. Moreover, our result suggested that sodium-glucose cotransporter 2 (SGLT2) inhibitors had lower risk of MACE compared with DPP-4 inhibitors. In large clinical trials, SGLT2 inhibitors statistically significantly decreased the risk of cardiovascular events compared with placebo in patients with type 2 diabetes at high risk for cardiovascular events. Although this may not be immediately relevant, our findings indicate that the same might be true in general type 2 diabetes population.

In Research 2, we reevaluated randomized, large event-driven trials with cardiovascular events as a primary end point in patients with type 2 diabetes by using an alternative measure to the HR, the difference in restricted mean survival time (RMST). It has been reported that DPP-4 inhibitors did not increase the cardiovascular risks compared with placebo in large placebo controlled clinical trials, and those results were confirmed in our study using the difference in RMST. On the other hand, it was reported that saxagliptin increased the risk of hospitalization for heart failure by 27% compared with placebo in a large placebo controlled clinical trial, but our results indicate that there

are no substantial differences in the risk of hospitalization for heart failure between saxagliptin and placebo. As for glucagon-like peptide 1 (GLP-1) receptor agonists and SGLT2 inhibitors, liraglutide, semaglutide, empagliflozin, and canagliflozin decreased the risk of MACE in each large clinical trial. Those results were confirmed in our study using the difference in RMST.

In order to clarify the overall picture for the cardiovascular risk of drugs for type 2 diabetes, not only conducting large prospective clinical trials in patients with type 2 diabetes at high risk for cardiovascular events but also various evaluations such as meta-analysis for general type 2 diabetes population and registry trials in real-world practice are needed. Also, in general, there is not one single and most appropriate measure to evaluate time-to-event data, and thus we believe that it is essential to assess the results of large clinical trials comprehensively by using various comparative measures.